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B 6
CLINICAL TRIAL ISSUES IN INTERMITTENT CLAUDICATION

B 6.1
Introduction

B 6.1.1
Scope of Section

Most clinical trials in IC relate to the use of pharmacological agents. Surgical treatment is rarely indicated in patients with IC and has not been the subject of comparative studies. A number of trials of exercise programs have been reported and are discussed in Basic Treatment (B 4.1.2, p S68). Some of the problems specific to these trials are discussed in that section and largely centre around the problem of blinding the patient and the observer as well as the problem of a suitable comparator treatment. Two comparative studies of angioplasty and exercise programs are also discussed in that section.

This chapter deals predominantly with the issues surrounding trials of pharmacological treatment. It does not attempt to be exhaustive but focuses on selected controversial aspects of trial methodology. Until recently, there have been remarkably few good studies looking at the methodology of such trials; for instance, it is only very recently that the relative merits of constant versus graded treadmill exercise has been investigated (see B 6.4.1, Constant Versus Graded Treadmill Protocol, p S112). Fundamental questions such as the reason for the day-to-day variability in treadmill walking distance, whether such variability is specific to a particular patient or whether patients with a very short claudication distance behave fundamentally differently from those with a long claudication distance, have not been fully investigated. There is therefore very little basis for making firm recommendations based on scientific evidence. **The Recommendations that follow are based largely on what is perceived to be the current best advice, rather than firm evidence. The Recommendations therefore could equally well be labelled as Critical Issues.**

B 6.1.2
Existing Guidelines for Clinical Trials in Intermittent Claudication

Over the years, a number of guidelines for clinical trials of pharmacotherapy in IC have been proposed by individual countries in Europe or by the new

European regulatory authority (Committee for Proprietary Medicinal Products; CPMP). International guidelines are sometimes an unhappy compromise between several different national views and rarely are supported by solid scientific evidence. National guidelines are often contradictory. In North America, no such guidelines have been promulgated. Further basic research into the methodologies involved are needed and ideally should be the basis of an international, or transatlantic, set of guidelines. The following Recommendations or advice are proposals based on extensive discussions among investigators experienced in this field.

B 6.1.3
Reporting Standards for Clinical Trials

Standardisation in reporting of results is crucial, and the Recommendations of the Committee on Reporting Standards of the Society for Vascular Surgery and the North American Chapter of the International Society for Cardiovascular Surgery[1] and the Technology Assessment Committee of the Society of Cardiovascular Interventional Radiology should be adopted (see also D 6, Clinical Trial Issues in Critical Limb Ischaemia, p S237).[2,3]

Recommendation 38: Reporting standards for trials in peripheral arterial disease
The recommendations of the committee on Reporting Standards of the SVS/ISCVS, and in the case of new devices the standards of the Technology Assessment Committee of the SCVIR, should be adopted where appropriate in all trials involving patients with peripheral arterial disease.

B 6.1.4
Aims of Trials in Intermittent Claudication

Trials of pharmacotherapy in patients with IC can look at four issues:

1. Does the new treatment significantly improve claudication distance?
2. Does the new treatment significantly alter the increased cardiovascular morbidity and mortality rates of patients with claudication?
3. Does the new treatment significantly improve quality of life?
4. Is the new treatment safe and free of important side effects?

The issue of safety must be incorporated into all trials, but in other aspects there is a fundamental difference between trials looking at a possible effect on walking distance and trials looking at cardiovascular morbidity and mortality rates. In the latter case, the end point of a fatal on nonfatal cardiovascular event will occur in only 4% to 6% of patients with IC per year (see A 2.4, Fate of Patients with PAD, p S14) ,and for a trial to have sufficient power, a large number of patients have to be recruited, usually several thousand. For similar reasons, the treatment period has to be relatively long, usually several years. Trials looking at pharmacotherapy for improving walking distance usually require only a few hundred patients, usually followed up for half a year. Issues relating to inclusion criteria will also be different. For instance, the initial ABPI is closely correlated with the risk of a subsequent cardiovascular event, but is probably unrelated to the likelihood of a new pharmacological treatment increasing walking distance.

There have been relatively few trials of pharmacotherapy in patients with IC for the prevention of cardiovascular events, the largest single trial being the CAPRIE trial, which involved nearly 6,000 patients with PAD in a total patient population of nearly 20,000.[4] The use of older antiplatelet agents for this indication is largely based on meta-analyses of a large number of small trials. The issues relating to trial methodology of pharmacotherapy for the prevention of cardiovascular events are not discussed here further. The following sections relate specifically to trials of pharmacotherapy aimed at improving walking distance.

B 6.2
Trial Design

There is general agreement that such trials have to be parallel group, double-blind, and randomised.

B 6.2.1
Comparator Drugs

The discussion of currently available pharmacotherapy for the treatment of claudication (p S76) suggests that it is inappropriate to use an active comparator drug, and therefore placebo-controlled trials are required.

B 6.2.2
Duration of Treatment and Follow-up

It is not possible to be specific on these issues, but in view of the fact that the symptom treated is chronic, it would seem reasonable to prolong treatment for several months. Six months is a widely accepted period.

A relatively short follow-up period, after treatment, would seem reasonable to ensure that there is no rebound or carry-over effect and possibly to establish whether continuing treatment is necessary to maintain any improvement. Most such claudication trials have not had a formal follow-up period, but 4 weeks of observation after treatment would seem reasonable.

Recommendation 39: Design of pharmacotherapy trials in intermittent claudication
Trials of pharmacotherapy to improve claudication distance should be double-blind, parallel-group, randomised, and placebo-controlled. Duration of treatment should be at least 6 months, and to exclude a sudden rebound effect, a post-treatment follow-up period of not less than 4 weeks should be considered.

B 6.3
Entry Criteria

B 6.3.1
Inclusivity Versus Exclusivity

This is a recurring controversy in all types of trials in patients with PAD, and indeed in many other diseases. The issue is whether an inclusive set of entry criteria is used to include a range of patients with different degrees of disease severity or a set of exclusive criteria that define a small, tight group of patients with very similar disease. Arguments in favour of exclusivity include:

1. Patients entered from a homogenous group.
2. Patients are clearly defined.
3. Differences between treatment and control group in terms of demographic or other characteristics, which theoretically may affect the treatment effect, are eliminated.
4. At least theoretically, the trial conditions are clearly defined and should be repeatable with similar results in other centres.

Arguments in favour of inclusivity are:

1. The more inclusive the study, the more it reflects real life.
2. Recruitment is easier, and fewer study centres are required.
3. More likely to reveal untoward side effects or drug interactions.
4. In practice, if the result of the study is positive, the drug is likely to be used in all patients with that condition—in this case, claudication. It therefore should be demonstrated to be effective in all patients, unless there is a good reason to exclude a particular subgroup.

Recommendation 40: Inclusivity versus exclusivity in selection of patients for clinical trials in peripheral arterial disease
On balance, it would seem that the advantages in favour of inclusivity are greater than those in favour of exclusivity, and therefore including a broader range of patients is recommended.

B 6.3.2
Stability and Natural History of the Disease

The natural progression of IC in individual patients is usually unpredictable (see A 2.4.1, Fate of Local Disease in the Legs, p S14). Ideally, patients should be stable before entry into the trial, but in practice most patients with IC fluctuate quite widely in the severity of their symptoms. It is therefore probably only practical to exclude patients in whom there is a recognised cause and expectation of rapid change during the treatment period. Patients with acute onset of claudication or within the first few months of the onset of claudication are widely believed to be particularly likely to fluctuate in their symptoms and should probably be excluded until the symptom is stabilised to some extent. The effects of any interventional treatment also often take several months to be fully apparent, and such patients should also be excluded meanwhile.

B 6.3.3
Optimal Background Treatment

This is probably more theoretical than practical, but it often gives rise to much discussion. The basic treatment of patients with IC is outlined earlier (p S66). There is no doubt that patients presenting with IC should have treatment of any coexisting disease, such as diabetes or hypertension. They also should be advised about appropriate changes in lifestyle, such as discontinuing smoking and maximising exercise. These measures should be taken *before* entering a patient into a trial of pharmacotherapy. This may have practical consequences, as in the treatment of hypertension, where initially there might be a deterioration in the walking distance because of a decrease in the central perfusion pressure. However, there is no good evidence that treatment of diabetes or cessation of smoking has any marked effect on claudication distance in the timespan of a few months.

The issue of exercise is more difficult. As discussed in section B4.1.2, Basic Treatment, there is good evidence that a supervised exercise program improves claudication distance, and clearly would be unethical to withhold this if it were available to the patient. (supervised exercise programs are not available in many centres, and many patients are unable or unwilling to participate. A pragmatic solution seems obvious; that, is taking all of the necessary measures that would normally be taken locally before entry into a trial of an individual patient and then continuing with the same advice and treatment throughout the duration of the trial.

B 6.3.4
Run-in Phase

The appropriate primary end point for such trials is some form of walking test (see B 6.4, End Points for Trials in Intermittent Claudication, p S112). However, as discussed previously, the walking distance of individual patients varies widely from day to day. There has therefore been a tendency to perform repeated walking tests at intervals (of, say, 1 week) and to exclude patients whose results fall outside preset limits (often ≥20% variation in absolute walking distance). Much of the argument about inclusivity and exclusivity applies to this issue as well; applying such entry criteria may exclude 10% to 30% of otherwise eligible patients. Furthermore, there is no good evidence that variance at the beginning of the study in terms of walking distance is related to a variance at the end of the study period. Nor does the evidence suggest that patients with a wide variance in walking distance behave fundamentally differently in response to pharmacotherapy to patients with a smaller variance. Furthermore, intersubject variability in these studies is almost always much greater than intrasubject variability, and therefore, the latter will have a relatively small effect on the accuracy of the final result.

A counter argument might be that patients with wide spontaneous variability in their walking distance may have a limiting factor other than claudication, and this may be a reason for the decision to define criteria for baseline treadmill test variability should be left to the investigators and sponsors responsible for a particular trial.

Recommendation 41: Entry criteria in clinical trials for pharmacotherapy and claudication
Before entry into a drug study, the patient's condition and walking ability should be relatively stable. In addition, all other routine measures for the treatment of the condition, such as antiplatelet therapy, normalising lipids, advising against smoking, exercise, and treatment of coexisting diseases, should have been instituted. These efforts should be documented, and patients should achieve a steady state for these variables before enrollment in a trial.
The extent to which entry variability of walking distance will affect the outcome of claudication studies is unknown, and therefore the question of whether to include stability testing on the treadmill should be left to the decision of the investigators and sponsors for the particular trial.

B 6.3.5
Stratification

There are two possible reasons for stratification:

1. To ensure comparability between the active and control groups in terms of demographic or other characteristics that may affect response to treatment
2. The possibility or probability that the treatment may be effective only in a subgroup of the total population

Neither of these reasons is sufficient to justify stratification in the particular context of pharmacotherapy for IC, unless there is some good prior information to suggest that the drug tested may only be efficacious in a particular type of claudicant. Theoretically, an infinite list of variables, ranging from age and gender to the presence of diabetes or the anatomic site of the atherosclerosis, could have an effect on the efficacy of the treatment tested. Stratifying for all these variables would be practically impossible. It is, of course, inevitable that even with randomisation there will be some demographic variable in which the two groups will be statistically significantly different. This cannot be avoided and does not matter, unless retrospective analysis shows that that particular variable was an independent determinant of efficacy. Furthermore, it is mathematically quite feasible and, if predetermined in the protocol, perfectly permissible to adjust the groups post-hoc if a particular demographic variable is found to be a significant determinant of efficacy.

Stratification is often used in clinical studies. If the patient population is sufficiently large to permit subgroup analyses, it does not significantly disadvantage the study. Stratifying because of the possibility that the new treatment may only be efficacious in a particular subgroup is illogical. If there is good prior evidence to suggest that a particular subgroup may behave differently, then the trial should be powered to be able to show this, and in reality one is performing two separate studies. These arguments apply for most of the criteria that have on occasions been used to stratify patients, such as the initial walking distance, presence of diabetes, or ABPI. There has been no reason to believe that any of the drugs tested so far in IC would only be effective in any particular subgroup, although this may not necessarily be the case for future drugs.

Recommendation 42: Stratification of patients in intermittent claudication pharmacotherapy trials
In general, there is no need to stratify patients enrolled in claudication pharmacotherapy trials. An exception would be in the case of pharmacotherapy that may be presumed to be more efficacious in one strata of patients as compared with another, in which case it may be more appropriate to conduct two separate trials. This may be the case in diabetic patients, for example.

B 6.4
End Points for Trials in Intermittent Claudication

The symptom treated is limitation of walking, and therefore the only appropriate end point is change in claudication distance. To standardise measurement of walking distance, a treadmill at a slope has traditionally been used.

B 6.4.1
Constant Versus Graded Treadmill Exercise Protocol

Initially, the treadmill had been used at a fixed speed and a fixed gradient and the distance or time measured until the onset of claudication, the ICD, or the maximum walking distance, that is, the ACD. The principal problem with the method has been the variability in the measurement from day to day. This probably only reflects the variability in claudication distance reported by patients in their everyday life. There is general agreement that some of the initial variability on the treadmill can be eliminated by familiarising the patient with the method. Most of these patients are elderly and have never been asked previously to walk on a treadmill. Therefore, one or two trial sessions on a treadmill should precede any actual measurement of walking distance used in a trial.

It is also the general impression that some variability in the results obtained with this method are attributable to the influence of the operator, particularly in relation to the instructions given to the patients tested. The end point is determined by the patient's interpretation of the sensation in the legs; it is necessarily subjective, and it is possible that this is to some extent influenced by the effect of the operator. It is therefore usually recommended that as far as possible the same operator should be used to test the same patient on different occasions.[5]

More recently, it has been suggested that a graded exercise schedule might be more accurate. In this, the treadmill is initially horizontal and then the slope is gradually increased at intervals, keeping the speed constant. This results in an increasing workload as the patient continues with the test and has long been routine practice in performing exercise ECG tests. The relative merits of a constant versus a graded treadmill exercise test have been discussed in detail in Basic Treatment (p S68). After an initial enthusiasm for the graded test, current evidence suggests that there is no significant difference in the reproducibility of the results obtained with the two tests.[6,7] Similarly, the initial suggestion that the "placebo" effect previously observed with constant exercise was not present with graded exercise has not been borne out by subsequent studies. "Placebo" effect in this context is probably a misnomer, because improvement in claudication distance almost invariably observed in the control group could be the result of a genuine spontaneous improvement in exercise tolerance of the patient rather than a true placebo effect.

B 6.4.2
Initial Claudication Distance Versus Absolute Claudication Distance

A number of studies have looked at the reproducibility of ICD and ACD, with most showing that the ACD is more reproducible and therefore presumably the more appropriate measurement to use as a primary end point.[6,7] It also has the theoretical justification that it probably more truly represents real life, where the patient is likely to continue to walk even after the first appearance of claudication discomfort, particularly because most doctors now routinely advise patients to walk into their claudication discomfort.

Recommendation 43: Primary end point in intermittent claudication trials—treadmill testing

- **The single primary end point that is most appropriate in intermittent claudication trials is the absolute claudication distance on a treadmill.**
- **Either graded or constant treadmill exercise is acceptable, but it is essential that they be performed in a rigorously controlled and standardised manner.**
- **If a patient has not used the treadmill before, then one or two familiarisation sessions before any definitive measurements are recommended, and it is also thought to be advantageous to try to ensure that the same operator supervises each test.**

B 6.4.3
Statistical Versus Clinical Significance

As with many artificial controversies, this is much debated. If the difference in the change in the walking distance in the treated and the control group is not statistically significant, then the result of the trial is negative, or unproven, whatever the size of the mean difference. The only issue is how large the statistically significant difference between two groups has to be to make it worthwhile administering the active treatment. As with all other forms of pharmacotherapy in medicine, this is a question of evaluating the cost/benefit of treatment, incorporating considerations of issues such as side effects, potential risks, and cost. The argument is often made that a relatively small, albeit statistically significant, improvement in active treatment of, say, 20% is unlikely to result in a significant improvement in the patient's quality of life. That is precisely why ideally changes in quality of life should be measured in these trials (see B 6.4.5, Measurement of Quality of Life, p S113).

There is perhaps some logic in deciding to analyse the data in terms of the number of patients who managed to achieve an arbitrarily set improvement in their walking distance—for instance, the number of patients who can increase their walking distance by 50% in the control group compared with the number of patients who can achieve a similar improvement in the treated group. It is generally agreed that in analysing the change in walking distance, a logarithmic scale rather than an arithmetic scale should be used.

B 6.4.4
Secondary End Points

Although it is generally agreed that there are no satisfactory surrogate end points in trials of pharmacotherapy in IC, strictly speaking,, the treadmill walking distance is also a surrogate end point. The patient does not complain of difficulty in walking on the sloping treadmill but has difficulty in going about their everyday business. However, the use of a treadmill is accepted as being close enough to the real situation and allowing a measurement to be made.

More "distant" end points, such as possible changes in plethysmographic blood flow or ABPI, may be measured and could give some useful clues about mechanisms of action, but they can in no way replace the measurement of the walking distance as a primary end point. Although there can be only one primary end point, there is no reason to limit other relevant measurements and events, which can all be secondary end points. This could include changes in ICD, noninvasive measurement of exercising blood flow, or reactive hyperaemia. Approximately 2% of the patients also develop some major cardiovascular event during a 6-month trial, and this clearly needs to be recorded. Apart from possibly giving a clue about mechanisms of action, such secondary measurements may also add robustness to the principal result of the primary end point.

B 6.4.5
Measurement of Quality of Life

If the quality of life, that is, the actual handicap to the patient, could be measured accurately, then in principle it would be the ideal primary end point. Unfortunately, we are very far from being able to do so. At least half a dozen different quality-of-life instruments have been used in patients with IC, but their validation is exceedingly difficult because there is no standard to which their accuracy can be compared.[5,8,9,10] Many quality-of-life instruments have been said to have been validated by using that term quite inaccurately. Such claims have been based on simply demonstrating reproducibility, which has nothing to do with true validation, or demonstrating a close correlation between the results of the quality-of-life measurement and the treadmill walking distance. This latter exercise is particularly futile: If a particular quality-of-life questionnaire could exactly reproduce the results of a treadmill walking test, then it would simply become another way of measuring walking distance and not a true measure of quality of life. Nevertheless, an accurate measurement of quality of

life should be the ultimate goal in such trials, and therefore some of the existing instruments should be used in all such trials to try and increase our understanding of this extremely important but very embryonic science.

Recommendation 44: Other end points in intermittent claudication trials

- **There are no appropriate surrogate end points for claudication distance, however measured, in trials of intermittent claudication.**
- **Other possibly relevant data should be collected because they will add robustness to any positive result and may give a clue regarding the mechanism of therapy action.**
- **Quality-of-life instruments should be used in all trials, and ultimately this may become a primary end point.**
- **Cost data should be documented over the duration of the trial.**

B 6.5
Trials of Prevention of Cardiovascular Morbidity and Mortality in Intermittent Claudication

The most serious risk for a claudicant is not the threat of requiring an amputation, which is approximately 2%, but rather the high incidence of nonfatal and fatal cardiovascular events, which occur in approximately 4% to 5% of claudicants per year. Prevention trials looking at modifying this systemic risk are relatively recent, and the methodology is still not fully developed. Entry criteria are usually very inclusive, encompassing all patients with symptomatic PAD and often also including patients who had PAD in the past but may now be asymptomatic as a result of some form of intervention. To obtain sufficient event rates and clinical relevance, such prevention trials are usually much longer than studies simply looking at walking distance. Two years or more is suggested. The same arguments apply for and against stratification, as in trials of walking distance.

An adequate end point in prevention studies is a composite end point comprising nonfatal ischemic stroke, myocardial infarction, cardiovascular death, and possibly coronary and carotid revascularisation and major amputation, whichever occurs first. As such, trials are inevitably multicentre and usually multinational. It is essential to standardise and verify the end-points. World Health Organisation criteria for the diagnosis of coronary events and strokes are usually adopted. In the optimal case, total mortality may be the most relevant end points; however this probably requires an exceptionally large number of patients. Combining nonfatal cardiovascular morbidity with all-cause mortality involves comparison of unequal entities. A combination end point using cardiovascular mortality has been criticised because survival, irrespective of the cause of death, is what ultimately matters. Such a concern may be mitigated if it can be shown that the results for the primary composite end point are statistically significant, that in the optimal case cardiovascular mortality is significantly reduced, and that the change in cardiovascular mortality also favourably influences all-cause mortality. There is probably little place in such trials for quality of life end points.

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